REMARKS

Claims 1, 4, 6-8 and 10-25 presently appear in this case. No claims have been allowed. Claims 1-4, 6-9, 14 and 15 have been withdrawn from consideration. The Official Action of September 1, 2006, has now been carefully studied. Reconsideration and allowance of all the claims now present in the case are hereby respectfully urged.

Briefly, the present invention relates to a method of treating a tumor in a subject by administering a composition that includes an agent that decreases the $[GSH]^2/[GSSG]$ ratio in the malignant cells of the tumor and an agent that maintains such a decreased ratio in the malignant cells of the tumor. The agents are administered such that the decreased ratio is maintained in the malignant cells continuously for about 15 to about 75 hours. The first agent is either an agent that oxidizes GSH or an agent that forms an adduct or a conjugate with GSH. The second agent is either an agent that inhibits the GCS enzyme, an agent that inhibits the GR enzyme, or an agent that diminishes the precursor of GSH. Precursors of any such agents may be substituted therefor.

The examiner has repeated the restriction requirement between Groups I and II and has made it final.

All of the present claims have now been amended to require the administration of at least two agents, which the examiner has designated as the Group II invention. Accordingly, all of the present claims are now directed to the present invention. Prompt consideration on the merits and allowance of all of the claims now present in the case are therefore respectfully urged.

The examiner has also repeated the species requirement and made it final. However, it is understood that, if the examiner finds the elected species to be allowable, that the remaining species will then be examined.

The examiner has acknowledged applicants' claim for foreign priority but has noted that a certified copy of the Israeli priority application has not been filed.

Applicants hereby withdraw their reliance for benefit on both the Israeli priority application as well as the PCT international application of which the present application was previously designated as a CIP. Attached hereto is a supplemental Application Data Sheet making the appropriate corrections.

Claims 11 and 13 have been objected to because the word “at” appears to be missing in line 1 of each.

Claims 11 and 13 have now been amended so as to correct this inadvertent error.

Claims 5, 10-13 and 16 have been rejected under 35 USC 112, 1st paragraph, as failing to comply with the written description requirement. The examiner states that to provide adequate written description and evidence of possession of a claim to genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The examiner states that the only common factor present with respect to the agents of the present invention are their biological activity and there is no description of structural characteristics that are required to retain such biological activity. The examiner states that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or synthesizing it; the compound itself is required. The examiner states that only the specific compounds disclosed in the specification by name are supported but not the full breadth of the claims. This rejection is respectfully traversed.

The examiner's attention is directed to MPEP ¶2163 II.A.3.(a).ii), relating to written description support for a claim drawn to a genus. There, the MPEP states that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. It goes on to state that a representative

number of species means that the species that are actually described are representative of the entire genus. Indeed, there are situations where even one species actually adequately supports a genus, citing, for example, *In re Herschler*, 591 F2d 693, 697, 200 USPQ 711, 714 (CCPA 1979). This section of the MPEP characterizes the holding of *Herschler* as follows:

> disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description.

In the *Herschler* case, the court relied on its previous decision in *In re Fuetterer,* 319 F.2d 259, 138 USPQ 217 (CCPA 1963). There, the claims were drawn to a rubber stock composition useful in producing tire treads that included a recitation of "an inorganic salt capable" of maintaining a homogeneous distribution of another component in the composition. The court stated, 319 F.2d at 265; 138 USPQ at 223:

> Appellant's invention is the combination claimed and not the discovery that certain inorganic salts

> have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is useful is useable in his combination. If others in the future discover what organic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure.

In discussing the fact situations in *Fuetterer* and in *Herschler*, the Herschler court made clear that there is a difference between the amount of written description disclosure necessary in cases wherein the applicant is claiming chemical compounds *per se*, and that necessary when the claims are drawn to the use of known chemical compounds in a manner auxiliary to the invention.

Here, the present claims are directed to the use of known chemical compounds in a manner auxiliary to the invention and there is no reason why applicants should not be permitted claims where these known chemical compounds are described by their functional properties. Thus, for example, in claim 1, (i) is an agent that oxidizes GSH. Applicant does not claim to have made any new invention with respect to the chemical compounds that oxidize GSH. Compounds that have

these properties are well known in the art and many of them are listed in the present specification, for example, at page 14, lines 17-25. The written description requirement does not require that applicants be limited to the list of specifically named compounds that have the property of being GSH oxidizing agents in cases such as this in which the identity of such agents is only auxiliary to the invention, which relates to a method of using a specific combination of such agents, administered in a particular manner. The same is true for agent (ii), which are listed at page 14, line 26, through page 15, line 23. The same is also true for the other listed agents. *In re Herschler* is specifically applicable to this case. The guidelines for application of the written description requirement as set forth in MPEP 2163 acknowledges that *In re Herschler* is still applicable law.

Accordingly, the present claims fully comply with the written description requirement of the first paragraph of 35 USC 112. Reconsideration and withdrawal of this rejection are respectfully urged.

Claims 5, 10-13 and 16 have been rejected under 35 USC 112, second paragraph, as being indefinite. The examiner states that the first recitation of an abbreviation in the claims must include the full meaning of the abbreviated term.

Claim 1 has now been amended to insert the meaning of [GSH] and [GSSG], as well as all other abbreviations, thus obviating this part of the rejection.

The examiner states that claim 5 recited the administration of "an effective amount" without conveying that the effective amount being administered is effective to treat the condition recited in the preamble.

Claim 1 has now been amended to specify that the amount being administered is "effective to treat the tumor." Accordingly, it is believed that this part of the rejection has also been obviated.

The examiner states that claim 5 refers to administering agents that decrease a certain ratio "in the malignant cells of said tumor." However, the examiner states that the preamble does not limit the treatment to malignant tumors.

Claim 1 has now been amended to specify that the tumors have malignant cells, thus obviating this part of the rejection.

Finally, the examiner states that claim 16 uses the terminology "from about 15 to about 75 hours." The examiner considers this to be indefinite because "from" implies a definite lower limit.

Claims 1 and 16 have now been amended to refer to maintaining the decreased ratio continuously "for about 15 to about 75 hours" (claim 1) or continuously administering the composition to the patient "for about 15 to about 75 hours" (claim 16). As the term "from about" no longer appears in the claims, this rejection has now been obviated.

Reconsideration and withdrawal of this entire rejection are therefore respectfully urged.

Claims 5, 10-13 and 16 have been rejected under 35 USC 103(a) as being unpatentable over U.S. patent 6,589,987 to Kennedy in view of Huang et al, Ali-Osman et al and Nagedra et al. The examiner states that Kennedy discloses that disulfiram inhibits the growth of cancer cells and that it can be administered in combination with another anti-cancer agent. The examiner states that Huang discloses that the GSH level in hepatocytes increases during active proliferation, and that GSH was found to be elevated in a number of tumor cell lines, which may change the thiol-redox status of the cell and affect the expression or activity of factors important for cell cycle progression. The examiner states that Ali-Osman discloses that depletion of GSH by BSO in malignant cells potentiated the cytotoxicity of BCNU. The examiner states that Nagendra discloses that chronic administration of disulfiram to rats affects GSH metabolism and that disulfiram perturbs the

GSH/GSSG redox status inducing oxidative stress on the brain. The examiner considers the instant claims to have been *prima facie* obvious from the above disclosures, stating that it would have been obvious to combine disulfiram, BSO and carmustine to treat tumors. This rejection is respectfully traversed.

The present invention is based on the discovery that raising the redox potential (E) above a threshold for a sufficient period of time will stop cell proliferation and, in the case of cancer cells, it will lead to apoptosis. This discovery is not disclosed or made obvious by any of the references of record. The present specification establishes that E must be held above the threshold long enough so that all the cancer cells enter phase G_{1pm} of the cell cycle because that is where they will get trapped if E is above the threshold. It follows from this that E must be maintained above the threshold for a full cell cycle plus the default time in G_{1pm} that triggers apoptosis. This requires that E be held high for several times the mean cell cycle period because the cell population has a wide spread of cycle periods, and many of them are greater than the mean. Thus, it is a very important aspect of the present invention that the decreased $[GSH]^2/[GSSG]$ ratio be maintained in the malignant cells continuously for about 15 to about 75 hours. See page 9, line

25, through page 10, line 18, of the present specification, for example.

It is known, in general, that the administration of an oxidant and/or an adduct former to effectively lower the concentration of GSH will in turn raise E. However, maintaining this raised E continuously for such a long period of time is not something that is disclosed by the prior art. While it may be possible to do so by continuously administering such an oxidant or adduct former for such a long period of time, this is not particularly practical. Accordingly, this leads to the further feature of the present invention whereby the decrease in the $[GSH]^2/[GSSG]$ ratio and, in turn, the increase in E, may be maintained even after the administered oxidant or adduct former is used up by preventing the cells from responding so as to lower E by manufacturing more GSH. This can be done by deactivating the CGS enzyme to prevent the cell from synthesizing *de novo* more GSH, and/or inhibiting the GR enzyme to prevent the cell from reducing GSSG to GSH.

While it is well known that deactivating CGS or GR will prevent the cell from restoring its GSH concentration, it is not obvious that this activity in combination with the initial decrease in the concentration of GSH by means of a GSH oxidant and/or adduct former will permit the $[GSH]^2/[GSSG]$

ratio to be continuously decreased for long periods of time without having to continuously administer the oxidant and/or adduct former. Furthermore, it was not known or obvious at the time the present invention was made, that, by maintaining this decrease for the required period of time, the malignant tumor cells will undergo apoptosis.

Accordingly, even if the examiner's thesis is accepted that it would be obvious to administer a combination of BSO, disulfiram and carmustine for the treatment of tumor cells, there is nothing in any of the references of record which would make obvious the claimed requirement that these agents be administered such that a decreased $[GSH]^2/[GSSG]$ ratio be maintained in the malignant cells continuously for about 15 to about 75 hours.

Furthermore, new claims 17-20 have been added that also are nowhere taught or suggested by any combination of the references of record. Claim 17 requires that the ratio that is maintained continuously for about 15 to about 75 hours is decreased by an amount such that E is increased by at least 10 mV during that period, or such that E is increased above E_{CCP} during that period. Preferably, E is increased to above about -200 mV during that period and, more preferably, to between -200 mV and -190 mV during such period. None of these parameters, which are preferred features of the present

invention, are taught or suggested by any combination of the references of record.

For all these reasons reconsideration and withdrawal of this rejection are respectfully urged.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By /rlb/
Roger L. Browdy
Registration No. 25,618

RLB:kg
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\B\BENA\HOFFMAN9\PTO\2007-01-03Amendment.doc